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Docket No.: PF-0459 US
Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1647

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Lal et al.

Title: HUMAN SIGNAL PEPTIDE-CONTAINING PROTEINS

Serial No.: 09/002,485 Filing Date: December 31, 1997

Examiner: Saoud, C. Group Art Unit: 1647

Box AF
Commissioner for Patents
Washington, D.C. 20231

REVISED BRIEF ON APPEAL

Sir:

Further to the Communication of 25 July 2001, submitted herewith are three copies of Appellants' revised Brief on Appeal. Appellants have addressed the issues of compliance under 37 C.F.R. 1.192(c)(5) (item 4 in the Communication of 25 July 2001). The Appeal Brief was further to the Notice of Appeal filed 5 March 2001 and received by the Patent and Trademark Office on 12 March 2001.

This is an appeal from the decision of the Examiner rejecting claims 24-27 and 29-33 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Genomics, Inc.), (Reel 9223, Frame 0216) who is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or are directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 24-27 and 29-33
Claims objected to:	(none)
Claims allowed:	(none)
Claims canceled:	Claims 2-14 and 19-21
Claims withdrawn:	Claims 1, 15-18, 22-23, 28, and 34-39
Claims on Appeal:	Claims 24-27 and 29-33 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

No amendments were made after the final rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to, *inter alia*, substantially purified polynucleotides encoding a human signal peptide-containing protein (SEQ ID NO:25) and to the use of these sequences for the diagnosis, treatment, or prevention of cancer and immunological disorders, toxicology testing, drug discovery, and disease diagnosis. As described in the specification at page 47, lines 6-20:

> Nucleic acids encoding the SIGP-25 of the present invention were first identified in Incyte Clone 1634813 from the cecal tissue cDNA library (COLNNOT19) using a computer search for amino acid sequence alignments. A consensus sequence, SEQ ID NO:102, was derived from Incyte Clones 1634813 (COLNNOT19), 2904583 (THYMNOT05), 1634813 (COLNNOT19), and 1310492 (COLNFET02), and shotgun sequence SAPA04436.
>
> In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:25. SIGP-25 is 150 amino acids in length and has one potential N-glycosylation site at N139; and five potential phosphorylation sites at T48, S118, S126, S135, and S136. SIGP-25 also has a potential signal peptide sequence encompassing residues M1-A23. SIGP-25 shares 28% identity with mouse beta chemokine, Exodus-2 (GI 2196924). The fragment of SEQ ID NO:102 from about nucleotide 175 to about nucleotide 235 is useful for hybridization. Northern analysis shows the expression of this sequence in gastrointestinal, developmental, hematopoietic,

and immunological cDNA libraries. Approximately 50% of these libraries are associated with fetal development/cell proliferation and 25% with immune response.

(6) ISSUE

Whether the use of SEQ ID NO:25 and SEQ ID NO:102 in toxicology testing, drug discovery, and disease diagnosis, satisfies the utility requirements of 35 U.S.C. § 101 and, derivatively, 35 U.S.C. § 112, first paragraph.

(7) GROUPING OF THE CLAIMS

As to the single outstanding issue, all claims on appeal are grouped together.

(8) APPELLANTS' ARGUMENTS

The Examiner's Rationale:

Claims 24-27 and 29-33 stand rejected under 35 U.S.C. § 101 as being drawn to an invention with allegedly no "apparent or disclosed specific and substantial credible utility." (Office Action dated 05 December 2000, page 4, paragraph 8). The Office Action further alleges that the asserted utility (*i.e.*, the use of SEQ ID NO:25 and SEQ ID NO:102 in the diagnosis, treatment, and prevention of cancer and immunological disorders) "would not be considered a specific, substantial, or credible utility to one of ordinary skill in the art at the time of the instant invention, absent evidence to the contrary, because the record fails to correlate the claimed invention with cancer or immunological disorders."

The Examiner also rejects the idea that expressed and annotated human polynucleotide and polypeptides are intrinsically useful for toxicology testing, drug discovery, and disease diagnosis. These utilities are dismissed on the basis that they do not constitute specific utilities for the claimed invention (page 6), they are only uses to the extent that the molecules are research tools (page 7), and there is allegedly no correlation of the instant polynucleotides and polypeptides with human diseases (page 8).

Argument:

The rejection of claims 24-27 and 29-33 is improper, as the claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue is a polynucleotide sequence (*i.e.*, SEQ ID NO:102) corresponding to a gene that is expressed in gastrointestinal, developmental, hematopoietic, and immunological tissues. Approximately 50% of the libraries from which the polynucleotides were isolated are associated with

fetal development/cell proliferation and 25% with immune response. The polypeptide encoded by SEQ ID NO:101 (*i.e.*, SEQ ID NO:25) is 150 amino acids in length and has one potential N-glycosylation site at N139; five potential phosphorylation sites at T48, S118, S126, S135, and S136, and a signal peptide sequence encompassing residues M1-A23. SEQ ID NO:25 shares 28% identity with mouse beta chemokine, Exodus-2 (Genbank ID g2196924; Hromas, R. *et al.* (1997) J. Immunol. 159:2554-2558). 3

Chemokines comprise a group of 8 to 14 kDa basic polypeptides that play a central role in immune system development, homeostasis, and function. Chemokines also affect the central nervous system as well as endothelial cells that are involved in angiogenesis or angiostasis. Members of the chemokine family of polypeptides are divided into 2 major subgroups, depending on whether they possess two adjacent cysteine residues (*i.e.*, the CC chemokines) or two cysteines separated by another amino acid residue (*i.e.*, the CXC chemokines). As polypeptides that specifically affect immune system development and function, there can be no question that these molecules can be involved in immunological disorders. Furthermore, chemokines are involved in tumorigenesis and metastasis. The role of chemokines in human disease has recently been reviewed by Rossi and Zlotnik [(2000) The Biology of Chemokines and their Receptors. Annu. Rev. Immunol. 18:217-242] who state that: 5

> Besides the role of chemokines and their receptors in angiogenesis, they also seem to be involved in the process of tumor cell migration, invasion, and metastasis. It is known that certain tumors exhibit certain patterns of metastasis (or invasion) to certain organs; in other words, tumor cells do not migrate randomly. One explanation for this phenomenon is that this specific migration of tumor cells may be determined by the chemokine receptors they express and by the chemokines expressed in the target organs. (Page 221.)
>
> Chemokines are likely to be primarily responsible for the cell infiltration observed in many disease states. The presence of proinflammatory chemokines may not be beneficial in a chronic inflammatory disease, but it is desirable in diseases where the immune response needs to be promoted, (*e.g.* cancer). In theory, any chemokine capable of inducing the migration of T, NK cells, dendritic cells, and/or macrophages could promote the regression or even eradication of a tumor mass by boosting the immune response against the tumor. Therefore, several chemokines are now being studied for their potential use as adjuvants in antitumor immune responses. Recent findings have demonstrated that IP-10, MIG, and Lptn have antitumor activity, as well as MCP-1, MCP-3, TCA-3 and others... (Page 223.)

Recent BLAST analysis provides additional evidence that SEQ ID NO:25 is a chemokine (enclosed). All of the top 20 BLAST hits are mammalian (mostly human) chemokines. SEQ ID NO:25 is 98% identical, from amino acid residue M1 to amino acid residue L150, to human TECK (thymus-expressed chemokine), a chemokine specifically expressed by thymic dendritic cells and potentially involved in T-cell development (Genbank ID g2388629; Vicari, A.P. *et al.* (1997) Immunity

7:291-301; attached).

The value of the bioinformatic approach for the identification of novel chemokines has been specifically addressed by Rossi and Zlotnik (*supra*):

> In the last few years, we have witnessed the development of EST (expressed sequence tag) databases and the widespread application of bioinformatics for new gene discovery. As a result, the pace of novel gene discovery has accelerated dramatically. One of the best examples of the impact of these technologies has been in the number of members of the chemokine superfamily identified in this time. **The chemokines are ideal molecules to be discovered through bioinformatics because they are small secreted molecules that exhibit very specific cysteine motifs in their amino acid sequence.** (Page 217.)

Based on the instant specification, and the knowledge available to one of ordinary skill in the art, the practioner would not doubt that SEQ ID NO:25 is a human lymphocyte-specific chemokine and, as such molecules, have numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease. While none of these uses necessarily require detailed knowledge of how the polypeptide coded for by the polynucleotide works, this is not the case with the instant invention. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Any of the above-identified uses meets the utility requirements of 35 U.S.C. § 101 and, derivatively, § 112, first paragraph. Under these sections of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The rejection fails to demonstrate either that the Appellants' assertions of utility are legally insufficient or that a person of ordinary skill in the art would reasonably doubt that they could be achieved. For these reasons alone the rejections should be overturned.

There is, however, an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law. These inconsistencies are discussed separately below.

I. The use of SEQ ID NO:25 and SEQ ID NO:102 for toxicology testing, drug development, expression profiling, and disease diagnosis and treatment are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There is a "well-established" use for the claimed invention, there are specific practical and beneficial uses for the invention, and those uses are substantial. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of human polynucleotides and their encoded polypeptides as tools for toxicology testing, drug discovery, and the diagnosis of disease is "well-established"

In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the invention at issue, are tools essential to any technology that uses expression profiling. Likewise, proteome expression profiling techniques have been developed in which the expression of numerous polypeptides is compared in two or more samples. Polypeptide or polypeptide fragments known to be expressed are tools essential to any technology that uses proteome expression profiling. See, *e.g.,* Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000).

The technologies made possible by expression profiling and the DNA and polypeptide tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. One of these techniques is toxicology testing, used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7):655, 656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153 (1999); Sandra Steiner and N. Leigh Anderson, *supra.*

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> ... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes.

> Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir *et al.* (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107(8):681 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening. This is true for both polynucleotides and polypeptides encoded by them.

There are numerous additional uses for the information made possible by expression profiling. Expression profiling is used to identify drug targets and characterize disease. See Rockett *et al.*, *supra*. It also is used in tissue profiling, developmental biology, disease staging, etc. There is simply no doubt that the sequences of expressed human genes all have practical, substantial and credible real-world utilities, at the very least for expression profiling.

Expression profiling technology is also used to identify drug targets and analyze disease at the molecular level, thus accelerating the drug development process. For example, expression profiling is useful for the elucidation of biochemical pathways, each pathway comprising a multitude of component polypeptides and thus providing a pool of potential drug targets. In this manner, expression profiling leads to the optimization of drug target identification and a comprehensive understanding of disease etiology and progression.

There is simply no doubt that the sequences of expressed human polynucleotides and polypeptides all have practical, substantial and credible real-world utilities, at the very least for biochemical pathway elucidation, drug target identification, and assessment of toxicity and treatment efficacy in the drug development process. Sandra Steiner and N. Leigh Anderson, *supra*, have elaborated on this topic as follows:

> The rapid progress in genomics and proteomics technologies creates a unique opportunity to dramatically improve the predictive power of safety assessment and to

> accelerate the drug development process. Application of gene and protein expression profiling promises to improve lead selection, resulting in the development of drug candidates with higher efficacy and lower toxicity. The identification of biologically relevant surrogate markers correlated with treatment efficacy and safety bears a great potential to optimize the monitoring of pre-clinical and clinical trials.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

There is no authority for the proposition that use SEQ ID NO:25 and SEQ ID NO:102 as tools for research is not a substantial utility, as the Examiner alleges at page 7 of the Office Action dated 05 December 2001. Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material

cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. As stated by Rossi and Zlotnik (*supra*):

> The chemokines and their receptors have received increasing attention in the last few years. Besides their role in HIV pathogenesis, it is now clear that chemokines participate intimately in many pathological conditions like inflammation and autoimmunity. They also play a very important role in normal homeostasis, including lymphoid development and migration. Some chemokines have potential therapeutic applications, mainly in cancer through their ability to attract subpopulations of lymphoid cells and also through their angiostatic effects... **We should expect advances (and surprises) to come from the chemokine field. It is one of the first molecular families on which we have witnessed the impact of bioinformatics and genomics. It is therefore also valuable to learn from these developments so that in the future we will be able to apply some of the lessons learned from the chemokines to other molecular families.** (Page 232, emphasis added.)

Thus, chemokines are **real** tools for drug discovery and the study of these molecules is not merely a academic pursuit. Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

B. The use of SEQ ID NO:25 and SEQ ID NO:102 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

Even if, *arguendo*, toxicology testing, drug development and disease diagnosis (through expression profiling) are not well-established utilities (which expressly is not conceded), the claimed invention nonetheless has specific utility by virtue of its use in each of these techniques. There is no dispute that the claimed invention is in fact a useful tool in each of these techniques. That is sufficient to establish utility for both the polypeptide and the polynucleotides encoding it.

Nevertheless, the claimed invention is rejected on the grounds that it does not have a "specific utility" absent a detailed description of the actual function of the protein expressed by the claimed nucleic acid or identification of a "specific" disease it can be used to treat. Apparently relying on the Training Materials, the rejection is made based on a scientifically incorrect and legally unsupportable assertion that identification of the family or families of proteins to which the claimed invention belongs, without more, does not satisfy the utility requirement. None of these grounds is consistent with the law.

1. A patent applicant can specify a utility without any knowledge as to how or why the invention has that utility

It is settled law that how or why any invention works is irrelevant to determining utility under 35 U.S.C. § 101: "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortright*, 165 F.3d, at 1359 (quoting *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340 (Fed. Cir. 1989)). *See also Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests."). It follows that the patent applicant need not set forth the particular functionality of the claimed invention to satisfy the utility requirement.

Practical, beneficial use, not functionality, is at the core of the utility requirement. *Supra* (introduction to § I). So long as the practical benefits are apparent from the invention without speculation, the requirement is satisfied. *Standard Oil* Co. v. *Montedison*, 664 F.2d 356, 374, 212 USPQ 327 (3d Cir. 1981); *see also Brana*, 51 F.3d at 1565. To state that a biological molecule might be useful to treat some unspecified disease is not, therefore a specific utility. *In re Kirk*, 376 F.2d 936, 945, 153 USPQ 48 (C.C.P.A. 1967). The molecule might be effective, and it might not.

However, unlike the synthetic molecules of *Kirk*, the claimed invention is **known** to be useful. It is not just a random sequence of speculative use. Because it is expressed in humans, a person of ordinary skill in the art would know how to use the claimed polynucleotide and/or polypeptide sequences -- without any guesswork -- in toxicology testing, drug development, and disease diagnosis regardless of how the polynucleotide or the protein it encodes actually functions. The claimed invention could be used, for example, in a toxicology test to determine whether a drug or toxin causes any change in the expression of lymphocyte-specific chemokines. Similarly, the claimed invention could be used to determine whether a specific medical condition, such as cancer, affects the expression of lymphocyte-specific chemokines and, perhaps in conjunction with other information, serve as a marker for or to assess the stage of a particular disease or condition.

In fact, the claimed polypeptide and/or polynucleotide sequences could be used in toxicology testing and diagnosis without **any** knowledge (although this is not the case here) of the protein for which it codes: it could serve, for example, as a marker of a toxic response, or, alternatively, if levels of the claimed polypeptide or polynucleotide remain unchanged during a toxic response, as a control in toxicology testing. Diagnosis of disease (or fingerprinting using expression profiles) can be achieved

using arrays of numerous identifiable, expressed DNA sequences, or by two-dimensional gel analysis of the expressed proteins themselves, notwithstanding lack of any knowledge of the specific functions of the proteins they encode.

2. A patent applicant may specify a utility that applies to a broad class of inventions

The fact that the claimed invention is a member of a broad class (such as DNA sequences or the proteins they encode expressed in humans) that includes sequences other than those claimed that also have utilities in toxicology testing, drug discovery, disease diagnosis, etc. does not negate utility as alleged by the Examiner at pages 6-7 of the Office Action. Practical utilities can be directed to classes of inventions, irrespective of function, so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. *Montedison*, 664 F.2d at 374-75. The law has long assumed that inventions that achieve a practical use also achieved by other inventions satisfy the utility requirement. For example, many materials conduct electricity. Likewise, many different plastics can be used to form useful films. *Montedison*, 664 F.2d at 374-75; *Natta*, 480 F.2d at 1397. This is a general utility (practical films) that applies to a broad class of inventions (plastics) which satisfies the utility requirement of 35 U.S.C. § 101.

Not all broad classes of inventions are, by themselves, sufficient to inform a person of ordinary skill in the art of the practical utility for a member of the class. Some classes may indeed convey too little information to a person of ordinary skill in the art. These may include classes of inventions that include both useful and nonuseful members. *See In re Ziegler*, 992 F.2d 1197, 1201, 26 USPQ2d 1600 (Fed. Cir. 1993). In some of these cases, further experimentation would be required to determine whether or not a member of the class actually has a practical use. *Brenner*, 383 U.S. at 534-35.

The broad class of steroids identified in *Kirk* is just such a class. It includes natural steroids (concededly useful) and man-made steroids, some of which are useful and some of which are not. Indeed, only a small fraction of the members of this broad class of invention may be useful. Without additional information or further experimentation, a person of ordinary skill in the art would not know whether a member of the class falls into the useful category or not. This could also be the case for the broad class of "plastic-like" polypropylenes in *Ziegler*, which includes many -- perhaps predominately -- useless members.

The PTO routinely issues patents whose utility is based solely on the claimed inventions' membership in a class of useful things. The PTO presumably would issue a patent on a novel and nonobvious fishing rod notwithstanding the lack of any disclosure of the particular fish it might be used

to catch. The standard being promulgated in the Guidelines and in particular as exemplified in the Training Materials, and being applied in the present rejection, would appear to warrant a rejection, however, on the grounds that the use of the fishing rod is applicable to the general class of devices used to catch fish.

The PTO must apply the same standard to the biotechnological arts that it applies to fields such as plastics and fishing equipment. *In re Gazave*, 379 F.2d 973, 977-78, 154 USPQ 92 (CCPA 1967) *quoting In re Chilowsky*, 299 F.2d 457, 461, 108 USPQ 321 (CCPA 1956) ("[T]he same principles should apply in determining operativeness and sufficiency of disclosure in applications relating to nuclear fission art as in other cases."); *see also In re Alappat*, 33 F.3d 1526, 1566, 31 USPQ2d 1545 (Fed. Cir. 1994) (Archer, C.J., concurring in part and dissenting in part) ("Discoveries and inventions in the field of digital electronics are analyzed according to the aforementioned principles [concerning patentable subject matter] as any other subject matter."). Indeed, there are numerous classes of inventions in the biotechnological arts that satisfy the utility requirement.

Take, for example, the class of interleukins expressed in human cells of the immune system. Unlike the classes of steroids or plastic-like polypropylenes in *Kirk* and *Ziegler*, all of the members of this class have practical uses well beyond "throwaway" uses. All of them cause some physiological response (in cells of the immune system). All of the genes encoding them can be used for toxicology testing to generate information useful in activities such as drug development, even in cases where little is known as to how a particular interleukin works. No additional experimentation would be required, therefore, to determine whether an interleukin has a practical use. It is well-known to persons of ordinary skill in the art that there is no such thing as a useless interleukin.

Because all of the interleukins, as a class, convey practical benefit (much like the class of DNA ligases identified in the Training Materials), there is no need to provide additional information about them. A person of ordinary skill in the art need not guess whether any given interleukin conveys a practical benefit or how that particular interleukin works.

Another example of a class that by itself conveys practical benefits is the G protein-coupled receptors ("GPCRs"). GPCRs are well-known as intracellular signaling mediators with diverse functions critical to complex organisms. They perform these functions by binding to and interacting with specific ligands. They are targets of many current drug treatments, including anti-depressants, anti-histamines, blood pressure regulators, and opiates.

Newly-identified GPCRs are used intensively in the real-world, even in cases where neither the

specific ligand that binds to the GPCR or the precise biological function of the GPCR is known. Newly identified GPCRs are used, for example, as toxicity controls for drug candidates known to bind other GPCRs. Because a person of ordinary skill in the art would know how to use any GPCR to achieve a practical benefit, even without any detailed or particular knowledge as to how it works, GPCRs as a class meet the utility requirement. There is simply no basis for the general statement made by the Examiner (Office Action, pages 11-12) to the effect that these molecules are not inherently useful by virtue of their important biological functions.

In fact, **all** isolated and purified naturally-occurring polynucleotide and polypeptide sequences which are expressible (*i.e.*, which are not pseudogenes that are never expressed during any natural biological process) can be and **are** used in a real-world context as tools for toxicological testing, e.g., for drug discovery purposes. This utility applies to all sequences actually expressed, yet in each case, the utility of the sequence is quite specific, e.g., insofar as it is used to detect its own specific complementary sequence in a sample containing many different sequences.

Lymphocyte-specific chemokines, like interleukins, GPCRs and fishing rods is a class that by itself conveys practical benefits. Unlike steroids and "plastic-like" polypropylenes, all of the lymphocyte-specific chemokines are expressed by humans, and all of them can be used as tools for toxicology testing. The claimed invention could be used, for example to determine whether a drug candidate affects the expression of lymphocyte-specific chemokines in humans, how it does so, and to what extent. The claimed invention has numerous other uses, including: stimulating lymphoid development, controlling lymphoid migration, stimulating lymphocytes to boost immune response, attracting or repelling lymphocytes to/from sites of infection, inflammation, or tissue damage, and repelling lymphocytes from tissues of the central nervous system following trauma. Just as there are no useless interleukins and GPCRs, there are no useless lymphocyte-specific chemokines. As these are practical, real-world uses, the application need not describe particular functionality or medical applications that would only supplement the utilities known to exist already.

C. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335

(6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

II. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

In addition to alleging a "specific" use for the claimed subject matter, a patent applicant must present proof that the claimed subject matter is in fact useful. *Brana*, 51 F.3d at 1565-66. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326, 206 USPQ 885 (CCPA 1980). "The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles and beliefs." *Id.* Unless there is proof of "total incapacity," or there is a "complete absence of data" to support the applicant's assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762.

A patent applicant's assertion of utility in the disclosure is presumed to be true and correct. *In re Cortright*, 165 F.3d at 1356; *Brana*, 51 F.3d at 1566. If such an assertion is made, the Patent Office bears the burden in the first instance to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See Langer*, 503 F.2d at 1391-92. If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The Revised and final Utility Guidelines are in agreement with this procedure. *See* Revised and final Interim

Guidelines at ¶ ¶ 3-4.

The issue of proof often arises in the chemical and biotechnological arts when the patentee asserts a utility for a claimed chemical compound based on its homology or similarity to another compound having a known, established utility. In such cases, the applicant can demonstrate "substantial likelihood" of utility by demonstrating a "reasonable correlation" between the utility -- not the function -- of the known compound and the compound being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895 (Fed. Cir. 1996). Accordingly, under *Brana*, the Patent Office must accept the asserted utility unless it can show that a person of ordinary skill in the art would reasonably doubt that a "reasonable correlation" exists. If the Patent Office makes such a showing, however, the applicant may submit evidence in support of the correlation.

In the present case, Appellants' invention is directed to, *inter alia*, substantially purified polynucleotides encoding a human signal peptide-containing protein (SEQ ID NO:25) and to the use of these sequences in toxicology testing, drug discovery, and disease diagnosis (see detailed description of the invention, above). SEQ ID NO:25 shares 28% identity with mouse beta chemokine, Exodus-2 (GI 2196924; Hromas, R. *supra*). Recent BLAST analysis provides additional evidence that SEQ ID NO:25 is a chemokine. All of the top 20 BLAST hits are mammalian (mostly human) chemokines and SEQ ID NO:25 is 98% identical, from amino acid residue M1 to amino acid residue L150, to human TECK (thymus-expressed chemokine), a lymphocyte-specific chemokine (Genbank ID g2388629; Vicari, A.P. *supra*). The only evidence of record shows that a person of ordinary skill in the art would not doubt that SEQ ID NO: 25, encoded by SEQ ID NO:102, is in fact a lymphocyte-specific chemokine, which is known to have a specific utility.

By ignoring the "reasonable correlation" requirement in the case law and failing to illustrate the procedure established by *Brana*, the Examiner has failed to set forth a proper *prima facie* case, and the rejection does not shift the burden of proof to Appellants for rebuttal. In fact, the rejection must be withdrawn, as the Examiner has failed to meet PTO's burden in the first place of establishing a proper rejection. There is no proper rejection for Appellants to rebut.

III. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific"

utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000)("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible, "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food" do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a

particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § I.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § I.B. Thus the Training Materials cannot be applied consistently with the law.

IV. To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

(10) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity" as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, to target rejections of claims to polypeptide and polynucleotide sequences where biological activity

information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This form is enclosed in triplicate.

Respectfully submitted,
INCYTE GENOMICS, INC.

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APPENDIX

Claims on Appeal:

24. An isolated polynucleotide encoding a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, and SEQ ID NO:77.

25. An isolated polynucleotide of claim 24 having a sequence selected from the group consisting of SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145,

SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, and SEQ ID NO:154.

26. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 24.

27. A cell transformed with a recombinant polynucleotide of claim 26.

29. A method for producing a polypeptide having a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, and SEQ ID NO:77, the method comprising:

(a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide of claim 24; and

(b) recovering the polypeptide so expressed.

30. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

(a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID

NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, and SEQ ID NO:154;

(b) a polynucleotide sequence complementary to (a); and

(c) an RNA equivalent of (a)-(b).

31. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 30.

32. A composition comprising a polynucleotide of claim 30 in conjunction with a suitable pharmaceutical excipient.

33. A microarray containing a fragment of at least one polynucleotide of claim 30, said fragment comprising at least 60 contiguous nucleotides of a polynucleotide of claim 30.